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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/898,566	07/02/2001	Terence C. Town	0152.00413	2721

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EXAMINER
SAKELARIS, SALLY A

ART UNIT	PAPER NUMBER
1634	7

DATE MAILED: 06/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/898,566	Applicant(s) TOWN ET AL.	
	Examiner Sally A Sakelaris	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group II, claims 17-20 and cancellation of Group I. Claims 1-16 in paper No. 6 is acknowledged. The traversal is on the ground(s) that the search and examination of Groups I and II would not involve a serious burden to the Examiner. However, it is maintained that undue burden would be required to examine the claims of Group I along with the claims of Group II as evidenced by the fact that the claims of Groups I and II have acquired a separate status in the art as recognized by their different classification and as recognized by their divergent subject matter and because a search of the subject matter of invention 1 is not co-extensive with a search of invention II.

The requirement is still deemed proper and is therefore made FINAL.

Acknowledgement of the provisional application drawn to this same subject matter has been made. The filing date of the instant Claims 17 and 18 is deemed to be the filing date of the provisional application 60/215,506 06/60/2000. The filing date of the instant Claims 19 and 20 is deemed to be the filing date of this current application 09/898,566 07/02/2001.

Claim Rejections – 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 17-20 are rejected under 35 USC 112, first paragraph, because the specification, while enabling for a marker comprising the OPRM1 +118A allele wherein the marker is indicative of risk for developing alcohol dependency, does not reasonably provide enablement for markers comprising the OPRM1 +118A allele wherein the marker is indicative of developing substance dependency wherein the substance is cocaine, marijuana, or substance dependency in its entirety. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claim 17 is broadly drawn to a marker comprising the OPRM1 +118A allele indicating the risk for developing substance dependency in its entirety. Claim 18 is drawn to a marker comprising the OPRM1 +118A allele indicating the risk for developing substance dependency wherein the substance is alcohol. Claims 19 and 20 are drawn to a marker comprising the OPRM1 +118A allele indicating the risk for developing substance dependency wherein the substance is cocaine or marijuana respectively. The specification teaches the testing for an association between DRD2 Taq1, a gene known to be associated with alcohol dependency, polymorphism and alcoholism and between OPRM1 + 118A/G polymorphism and alcoholism by genotype or allele. In this study, it is taught that there is a significant association between OPRM1 +118A/G polymorphism and alcoholism, both by genotype and allele. The

specification further teaches the lacking association between both gender and ethnicity and DRD2 or OPRM1 polymorphism for the risk of alcoholism. The specification teaches their study subjects comprising; 102 individuals meeting the criteria, as defined in DSM IV, for alcohol dependency, 179 meeting this same criteria for alcohol dependency and who reported alcohol as the primary drug of dependency, and 43 cases within the 179 with a history of abuse of other substances("alcohol, nicotine and primarily cocaine and marijuana included") and current daily use of cigarettes. The specification further teaches that, "there is a consistent and orderly trend for higher frequencies of the AA genotype and A allele in groups with increasing numbers of substances used"(Page 11, line 6-7). However, the specification does not teach an association of cocaine and marijuana dependencies and the OPRM1 +118A/G polymorphism. Furthermore, no association studies similar to those reported above for alcohol dependency and the OPRM1 +118A/G polymorphism were done to further elucidate the same association but with reference to cocaine and marijuana dependencies. The ability to establish a correlation between OPRM1 +118A allele and cocaine and marijuana dependency is highly unpredictable and can only be determined through extensive, random, trial and error experimentation. The prior art corroborates the unpredictability that exists in the art for establishing a correlation between the OPRM1 alleles and substance dependency. For example, (Neurobiology (1998) 95: 9608-9613) states that, "β-endorphin has been postulated to play a role in diverse biological functions…β-endorphin can regulate the secretion of both stress and reproductive hormones, thereby influencing a variety of physiological functions"(9613). Furthermore, considering that "the A118G polymorphism may change the receptor with respect to the binding affinity of β-endorphin…suggesting that individuals carrying the variant receptor gene (A118G) may show

differences in some of the functions mediated by OPRM." The art states that for example, "response to stress, reproductive function, and pain perception could be altered...as well as...significant effects on the susceptibility or vulnerability to develop multifactorial diseases such as specific addictions"(9613). Furthermore, the post filing date art corroborates the unpredictability that exists in the art for establishing a correlation between the OPRM1 alleles and substance dependency. For example, (Molecular Psychiatry (2002) 7, 224-228) states that "genetic association studies investigating the role of the +118A allele of the human μ-opioid receptor gene in risk for alcohol dependency have produced inconsistent findings, possibly because of the failure to recognize sampling methodology difficulties inherent in association studies of polygenic disorders"(224). The art further states that "the search for candidate risk genes in substance abuse...have underscored the methodological difficulties in association studies of polygenic disorders"(224). Therefore, neither the specification nor the art enable establishing a correlation between the OPRM1 alleles and substance dependency. The specification itself, reveals the applicants speculation that "the dependency on other addictive substances is similar to alcoholism and therefore applicants determined that an assay for alcoholism would also function for diagnosing a predisposition to other substance dependencies"(Page 4, line 25-27). The sheer fact that "the dependency on other addictive substances is similar to alcoholism" does not provide the necessary enablement for the applicants claims to allow for diagnosing a predisposition to other substance dependencies. As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as

well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, one cannot readily anticipate a correlation between the OPRM1 +118A polymorphism and the risk of developing substance dependency wherein the substance is cocaine, marijuana, or broadly, any substance dependency because there is insufficient evidence provided in the specification to establish that the findings obtained with alcohol dependency can be extrapolated to all types of substance dependency. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 17-20 are indefinite and vague over the recitation of "marker" because the claims do not set forth the identity of the polynucleotide "marker." For example, it is unclear

whether the "marker" as stated in the claims represents the allele as a whole (eg. the complete OPRM1 gene or a cDNA comprising the +118A polymorphism), a smaller fragment thereof (eg. a fragment consisting only of the A at position +118), or a larger fragment of the OPRM1 gene containing the +118 allele. The claims should be amended to clarify exactly what is intended to be claimed by using the term "marker."

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Bond et al., *PNAS* 1998 **95**, 9608-9613.

The claims are broadly drawn to a marker for determining the risk of developing substance dependency comprising the OPRM1 + 118A allele. Bond et al. teach the "identification of different single nucleotide polymorphisms (SNPs) in the coding region of the mu opioid receptor gene," the primary site of action for the most commonly used opioids, the most prevalent SNP is a nucleotide substitution at position 118 (A118G)"(Bond et al, page 9608). Furthermore, the reference teaches "the A118G variant receptor binds β-endorphin, an endogenous opioid that activates the mu opioid receptor, approximately three times more tightly than the most common allelic form of the receptor." As a whole, the reference teaches that "SNPs in the mu opioid receptor gene", as exemplified by A118G, "can alter binding and signal transduction in the resulting receptor and may have implications for normal physiology, therapeutics, and

vulnerability to develop…addictive diseases"(Bond et al., page 9608). In particular, Bond teaches isolated nucleic acids comprising an A at nucleotide position +118 of the coding region of the OPRM1 gene and purports that the polymorphism "may have implication for normal physiology, therapeutics, and vulnerability to develop or protection from divers diseases including the addictive diseases"(Page 9608). Therefore, all of the limitations of the instant claim are anticipated by Bond et al..

In addition, with respect to Claims 17-20, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In the instant case, the SNP at position 118(A118G) taught by Bond et al. is no different from the instantly claimed marker for determining the risk of developing substance dependency comprising the OPRM1 + 118A allele(see MPEP 2111.02). Furthermore, it is noted that the claims are broadly drawn to markers comprising the OPRM1 +118A allele. The specification does not clearly define what constitutes a "marker" and the claims do not clearly define the structure and length of the marker. Therefore, the claims read on any marker comprising the "A" at nucleotide position +118. Bond et al. further teach primers comprising an "A"(pg. 9609) and thereby the primers of Bond meet the limitations of claims 17-20.

7. Applicant should note that 16 out of the 23 references cited in IDS(Rec'd 9/17/2001) were not provided to the examiner and as a result, were not reviewed.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Friday from 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantai Dessau whose telephone number is (703)605-1237.

6/6/02
Sally Sakelaris

CARLA J. MYERS
PRIMARY EXAMINER